REMARKS/ARGUMENTS

In this Amendment, claims 22, 43, 44, 58 and 59 are currently amended and claims 23-42, 45-57 and 60-61 are pending as previously presented. Claims 1-21 are canceled without prejudice or disclaimer. Claims 62-68 are newly presented.

It is submitted that no new matter is introduced into the application by virtue of amended and new claims. More specifically, amended claims 22, 43, 44, 58 and 59 are supported by the instant specification, *inter alia*, for example, on page 7, lines 3-13 and on page 8, lines 18-26. Support for new claims 62-64 and amended claims 44-57 is found in the instant specification on page 10, lines 3-10, which disclose the suitability of the present invention for both multidose dry powder inhalers and for predosed units of individual powder doses, e.g., capsules, which can be dispensed from single dose dispensers and/or reservoirs, as understood by those having skill in the art. Support for new claims 65-68 is found in the instant specification on page 8, lines 36-39, as well as in the examples, for example, pages 17-18 and Table 1 and pages 19-20 and Table 2. Because the added claims more concisely define the subject matter of the invention and are fully supported by the specification of the application as filed, it is respectfully submitted that a new or further search should not be required.

The presently pending claims are thus claims 22-68.

The claims fulfill the requirements of 35 U.S.C. §103(a)

Claims 22-61 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Staniforth (Respiratory Drug Delivery II) in view of Carling (WO 93/11773).

The Examiner characterizes Staniforth as disclosing "a delivery of powders to the respiratory tract, where the particles have a diameter of from about 1 to 3 micron" and "the particles are said to be adhered to a large carrier particle of the size 200 micron." The Examiner further states that "Staniforth discloses that additives such as magnesium stearate and talc are added to the fine particles adhered to coarse carrier particles of sucrose crystals, and that Staniforth teaches active particles such as salicylic acid, but lacks disclosure on other active agents." The Examiner characterizes Carling as teaching "formulations of formoterol

(as a fumarate dehydrate) and budesonide for inhalation in the treatment of respiratory disorders." The Examiner further states that Carling teaches that "formulations may be in the form of a dry powder and administered by a dry powder inhaler" and that "the carrier such as lactose, dextran or glucose and other additives are added to the powder formulation."

In view of the above characterization of the cited art, the Examiner opines that it allegedly "would have been obvious to a person of ordinary skill in the art at the time of the invention, given the general formulations of Staniforth of powder formulation comprising an active agent in small particle size and a carrier particle in large size and magnesium stearate as an additive, to have looked in the art for specific active agents with reasonable expectations of successfully preparing effective dry powder formulations comprising the active agents which can be used in treating other respiratory disorders and other patients."

Applicants respectfully disagree with this characterization of the cited art and traverse the present rejection. It is respectfully submitted that Applicants' presently claimed invention is neither the same as, nor obvious in view of, the disclosure of Staniforth combined with that of Carling.

It is well understood that the presently claimed invention must be considered as a whole in determining differences between the prior art and the presently claimed invention. M.P.E.P. §2141.02. In addition, all claim limitations must be taught or suggested by the cited art reference. M.P.E.P. §2143.03. Additionally, it is well established that a reference must be considered for all that it teaches, i.e., as a whole and in its entirety. This includes a consideration of portions that would lead away from the claimed invention. *W L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed.Cir. 1983), as cited in the MPEP §2141.02. Specific sentences should not be taken out of context from prior art references; all of the teachings of the reference must be considered to determine what the reference really teaches. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.* 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986). Furthermore, combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is improper. *ACS Hospital Systems, Inc. v. Montifiore Hospital,* 221 USPQ 929, 993 (Fed. Cir. 1984). Absent some teaching, suggestion, or incentive supporting the combination,

obviousness cannot be established by combining the teachings of the prior art. *In re Geiger*, 815 F.2d 686, 688 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

The present invention is directed to dry powder formulations and methods of making dry powder formulations with improved moisture resistance for use in inhalers. Applicants' formulations comprise a pharmaceutically inactive carrier, a pharmaceutically active component comprising at least one finely-divided pharmaceutically active compound comprising particles of inhalable size and magnesium stearate, in an amount effective to provide the dry powder formulation with reduced sensitivity to penetrating moisture. The admixture of carrier, active component, and magnesium stearate as ingredients in Applicants' dry powder formulation is especially suitable for use in dry powder inhalers or devices containing a powder reservoir that is typically subject to the adverse effects of moisture, because there is not a water-tight seal to prevent the components of the formulation from absorbing water vapor that gets in. Examples of such inhalers or devices include multidose dry powder inhalers or inhalers for predosed units, such as capsules. The infiltration of water vapor into these inhalers and devices results in a dramatic fall in the inhalable portion of the released dose of the active component, e.g., the fine particle fraction or FPF.

In contrast to the present invention, Staniforth's cited meeting presentation paper is directed to a study of the properties and the complex forces and interactions that bind particles together in dry powder formulations. Staniforth is concerned with and describes the preparation of agglomerates of particles that optimally break up into primary particles, particularly on entering the airways of the lungs. (See, e.g., pages 533-534 of Staniforth). Staniforth discloses physical conditions for adhesive forces between two unlike particles and the manipulation of inter-particle force interactions with the aims of, on the one hand, producing agglomerates of drug particles and, on the other hand, allowing liberation of the drug particles from the agglomerates. Staniforth discloses physical aspects of particle size, shape and texture, as well as the particulars of particle force interactions to achieve these aims. (See, e.g., pages 535-545 of Staniforth).

Staniforth more specifically discloses that the addition of a "third component" to a pre-formed mixture of salicylic acid and sucrose can influence the physical stability of ternary

mixtures in a different manner as a result of charge interactions among the components. On page 546 of the cited paper, Staniforth states that the addition of magnesium stearate and talc as third components adversely affected the adhesion of salicylic acid particles to the sucrose carrier crystals. According to Staniforth, the addition of magnesium stearate "disrupts bonding and liberates the drug particles at reduced removal forces."

Staniforth's disclosure merely proposes that magnesium stearate is a material that reduces the adhesive forces between salicylic acid and sucrose. This proposal does not remotely suggest Applicants' discovery that magnesium stearate is useful for preparing stable, inhalable dry powder formulations with reduced moisture sensitivity, and for being employed as an ingredient in the dry powder formulation housed in a dry powder inhaler. There is no teaching or recognition by Staniforth that if the interaction of magnesium stearate with the other components is too destabilizing, the fine particles of salicylic acid would detach from the sucrose during storage and would agglomerate due to electrostatic forces. As a consequence of this, the fine particle fraction (FPF) of an emitted dose would be dramatically reduced.

In addition, unlike Applicants, Staniforth does not teach or appreciate that the ternary component must be sufficiently destabilizing so as to aid the dissociation of the active compound particles and the carrier particles as the dose is released, but not so destabilizing as to release the active compound particles during storage. Unlike Applicants, Staniforth is completely silent and does not recognize the need to achieve and use an amount of magnesium stearate that results not only in the dissociation of active particles and carrier particles when an inhaler or inhaled dose is involved but also in the non-dissociation and stabilization of active particles during storage.

On page 546 of his paper, Staniforth describes an experiment that is also depicted in Fig. 6 of this same paper. Applicants note that the description of Fig. 6 and the figure itself present a confusing and unclear teaching, at best. According to the text at page 546, Fig. 6 "shows the effect of additives such as magnesium stearate and talc added separately to a mixture of fine salicylic acid particles adhered to the surface of coarse sucrose crystals." The text goes on to describe Fig. 6 by stating that "... whilst talc stabilizes the adhesive units, the

presence of magnesium stearate disrupts bonding and liberates the drug particles at reduced removal forces. ..."

However, what is actually shown in Staniforth's Fig. 6 graph is the separate addition of talc and starch, which are described as being "third component particles". These third component materials are independently and separately added to already-formed "binary mixes" of sucrose and salicylic acid to determine the effect(s) on the physical stability and adherence properties of the sucrose and salicylic acid components of the mixes. Consequently, in view of the ambiguous teachings of Staniforth's text and the accompanying Fig. 6, it is not clear to one skilled in the art whether magnesium stearate or starch is the third component that is used and has the described effects.

Carling teaches a combination therapy for the treatment of a respiratory disorder, such as asthma, in which formoterol and budesonide, or suitable salts of these components, are administered together by inhalation. Although Carling discloses that the formoterol and budesonide combination formulations may be dispensed using a dry powder inhaler, such as a TURBUHALER, there is no remote teaching or suggestion in Carling to use magnesium stearate in admixture with the other ingredients in the formulation for inhalation to reduce moisture sensitivity and to stabilize the formulation.

Considering the cited references for all that they teach, it is submitted that the combination of Staniforth's teachings with those of Carling would not lead the skilled practitioner at the time of the present invention to include magnesium stearate as an integral component in an inhalation formulation with a reasonable expectation of successfully stabilizing a dry powder formulation and improving its resistance to moisture. The reasons for this are clear. First, Staniforth's disclosure teaches that magnesium stearate added as a ternary component to a binary mixture destabilizes the adhesion of salicylic acid particles to sucrose carrier particles comprising the binary mixture. In addition, there is no teaching or appreciation by Staniforth that, for the purposes of a dry particle inhaler, if the magnesium stearate interaction is *too* destabilizing, the fine particles of salicylic acid as active would detach from the sucrose crystals during storage and would agglomerate, thereby adversely

affecting, as well as significantly reducing, the FPF of any dose that is emitted from the inhaler. Staniforth does not teach a stabilized FPF and dry powder formulation for an inhaler.

Further, there is no teaching or suggestion in the combination of Staniforth and Carling that would lead one skilled in the art to use magnesium stearate in a dry powder formulation, such as a formulation disclosed in Carling, in an amount effective to reduce sensitivity of the dry formulation to moisture. In addition, one skilled in the art would not be led to combine Staniforth's teaching with that of Carling so as to achieve a stabilized, inhalable and magnesium stearate-containing dry formulation having both reduced sensitivity to moisture and stability during storage in an inhaler without additional types of moisture-proofing. Absent a teaching, suggestion, or incentive in the art to support the combination, obviousness cannot be established.

Combining Staniforth's academic teaching with Carling does not lead one to arrive at Applicants' newly discovered stabilized, magnesium stearate-containing, dry powder formulation with reduced sensitivity to penetrating moisture for a dry powder inhaler. Staniforth discloses a destabilizing effect upon the addition of magnesium stearate to a dry particle formulation comprising sucrose and salicylic acid. This teaches away from the presently claimed invention which requires a formulation in which the magnesium stearate component provides both a moisture reducing and a stabilizing effect, and in which the components are present in amounts that provide optimum inhalability of the FPF during inhaler use, as well as storage stability of the dry formulation when the inhaler is not in use. Further, in contrast to Applicants' invention in which magnesium stearate is an integral component in the dry powder formulation to improve moisture sensitivity of the dry powder formulation, the TURBUHALER device disclosed by Carling and described in Carling's examples involves the use of a desiccant that is separate from and external to the formulation to be inhaled.

Staniforth's equivocal disclosure and Fig. 6 information do not lead one skilled in the art to know or understand that magnesium stearate is useful or suitable as a moisture reducing component in a dry powder formulation for an inhalation device. Rather, Staniforth merely discloses that magnesium stearate (or starch according to Fig. 6) is added to a binary mixture in a model formulation to test *in vitro* various theories of molecular interaction that are posited in

the paper. Staniforth is silent regarding whether or not a magnesium stearate/salicylic acid/sucrose formulation (or a starch/salicylic acid/sucrose formulation) is suitable for a dry powder inhaler and/or affects the moisture content of the formulation in an inhaler. Staniforth is also silent as to whether the destabilizing effect of magnesium stearate (or starch) on the salicylic acid/sucrose mixture is a positive or a negative result for a formulation containing these ingredients when placed in a dry powder inhaler. Carling's disclosure of dry powder formulations involving carriers such as lactose, dextran, or glucose and dispensers such as the TURBOHALER neither teaches the use of magnesium stearate to stabilize such formulations nor addresses the destabilizing and potentially adverse effects of magnesium stearate in the formulations.

It is further submitted that the presently claimed invention provides a new and unexpectedly successful solution to the art-recognized problem of moisture's adverse effects on dry powder inhalable formulations and allows the efficient operation of inhaler devices that dispense dry powder formulations, which are stored over time between uses. Applicants' presently claimed invention comprising active component, carrier and magnesium stearate surprisingly reduces the sensitivity of a dry powder formulation to moisture. The intimate association of the active component, carrier and magnesium stearate in the dry powder formulation would not be reasonably expected *a priori* to lead to a suitable mixture for inhalation. This is because, at the time of the invention, the ordinarily skilled person in the art would not have been led to consider the use of magnesium stearate in inhalation formulations and devices. Instead, other means to reduce moisture in dry powder formulations were used in the art, as is discussed further below.

In particular, at the time of the present invention, the art taught a general avoidance of magnesium stearate for inhalation. Examples of such teachings are provided in the enclosed three documents, which demonstrate that, at the time of the invention, the art generally cautioned against the inhalation of magnesium stearate powders, thus providing a lack of impetus for the artisan to arrive at Applicants' presently claimed invention. The first document is page 1442 from Martindale, *The Extra Pharmacopeia,* 28th Edition, Ed. Reynolds, J.E.F., London, The Pharmaceutical Press, 1982, (Tab 1), in which adverse effects of inhalation of magnesium stearate are mentioned in column 1. The second document is a 1998 Material

Safety Data Sheet from Spectrum, a manufacturer of magnesium stearate, (Tab 2), which points out hazards related to the inhalation of magnesium stearate. The third document ("Magnesium Stearate", authored by LV Allen and PE Luner, In: *The Handbook of Pharmaceutical Excipients*, 2nd Ed., 1994, pp. 280-282; Tab 3) provides factual information regarding magnesium stearate and indicates on page 281 that inhalation of magnesium stearate powder is harmful.

Thus, if one ordinarily skilled in the art had considered combining magnesium stearate with an inhalable dry powder formulation in an inhaler device at the time of the present invention, she/he would have dismissed the combination due to the negative implications surrounding the use of magnesium stearate as an inhalant. Accordingly, the combined teachings of the cited references and the general state of the art at the time of the present invention would not have led one having ordinary skill in the art at the time to achieve Applicants' invention with a reasonable expectation of success. It is Applicants' surprising findings and invention that provided the art with methods and products that included magnesium stearate for inhalable dry powder formulations comprising FPFs, in an amount effective to reduce the moisture sensitivity of the formulations and to increase their stability.

Additionally and in support of the above, the art at the time of the present invention taught and provided other solutions to overcome the problem of keeping powders in multidose reservoir devices in a dry, flowable, and readily and reliably dispensable state. One typical solution to the problem of moisture resistance at the time is found in the TURBUHALER device, disclosed and employed by Carling (See, e.g., Example 1, page 7 of Carling), which includes a discrete desiccant material that is kept external to the powder formulation that is to be delivered by inhalation. A schematic depiction of the design of a TURBUHALER device with its external desiccant is presented in the attached document, taken from K.I. WeHerlin, "Design and Function of the Turbuhaler®", In: *A New Concept in Inhalation Therapy*, Eds. Newman, S.P., Moren, F. and Crompton, G.K., (1987):85-89. (Tab 4). Thus, it is clear that Carling's teaching and use of the TURBUHALER device, combined with Staniforth's disclosure of the destabilizing effects of magnesium stearate used in *in vitro* interactions with salicylic acid and sucrose, would not lead one skilled in the art to arrive at Applicant's

presently claimed invention, particularly in view of the general sentiment in the art at the time, which did not advocate inhalation of magnesium stearate.

Applicants' presently claimed invention provides a novel solution to the serious problem of moisture's adverse effects on inhalable dry powder formulations administered from reservoirs and devices that house these dry powder formulations, e.g., predosed units such as capsules and multidose units. Applicants' invention allows such formulations to withstand the deleterious effects of moisture on the stored dry formulations over time without resorting to inhalers that require a physical separation of the dry formulation from a moisture-preventing material. The combination of Staniforth and Carling does not teach or recognize this problem, or the solution to this problem in the art. Furthermore, Staniforth and Carling, in combination, do not teach a dry powder formulation comprising, in admixture, active component, carrier and magnesium stearate, with magnesium stearate present in an amount effective to achieve reduced moisture sensitivity of the resulting dry powder formulation and the FPF therein, as well as stability during storage. Due to the inadequacies of their teachings, the combination of Staniforth with Carling would not result in a dry powder formulation containing active ingredient, carrier and a moisture reducing and stabilizing amount of magnesium stearate housed together in an inhaler device that does require a separate and external desiccant component.

In consideration of the foregoing, it is submitted that Carling does nothing to compensate for the deficiencies that are endemic to the cited Staniforth paper. Therefore, combining the teaching of Staniforth with that of Carling would not achieve Applicants' presently claimed invention. Based on these teachings, the skilled practitioner would not be led to make the modifications necessary to arrive at the presently claimed invention with a reasonable expectation of success.

Accordingly, it is respectfully submitted that a *prima facie* case of obviousness has not been established based on the combination of Staniforth and Carling. The presently claimed invention, considered in its entirety, is distinct from and unobvious over the cited combination of these references. Accordingly, withdrawal of the §103(a) rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that this application is now in condition for allowance. An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this Amendment and terminal disclaimer, or during the pendancy of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. **50-0311**, Reference No. **28069-606-CON**, Customer No. **34537**.

Should any additional extension of time be required for the timely consideration of this Amendment and response, the Commissioner is hereby authorized to grant any such extension of time as may be necessary, and to charge any additional fee(s) owed by Applicants for such extension of time, to the above-mentioned Deposit Account, Reference and Customer Numbers.

If the Examiner believes that further discussion of the application would be helpful, the Examiner is respectfully requested to telephone the undersigned at (212) 692-6742 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

Respectfully submitted,

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.

Date: September 20, 2005

By: Leslie A. Serunian
Leslie A. Serunian
Registration No. 35,353

Correspondence Address:
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
The Chrysler Building, 24th Floor
666 Third Avenue
New York, New York 10017
Telephone: (212) 935-3000
Facsimile: (212) 983-3115
Direct Tel.: (212) 692-6742

MARTINDALE: the Extra Pharmacopeia, 28TH ED.
Reynolds JEF, ed. London, the Pharmaceutical Press

lacquered.
Buffered Cream Aqueous (*A.P.F.*) has a similar formula with glycerol 5%.

Emulsifying Ointment (*B.P., A.P.F., Ind. P.*). Emulsif. Oint.; Ung. Emulsif. Emulsifying wax 3, white soft paraffin 5, and liquid paraffin 2, all by wt. Store at a temperature not exceeding 25°.

Emulsifying Ointment Soap (*Roy. Hallamshire Hosp.*). Emulsifying wax 80 and white soft paraffin 20. For use as a soap substitute in eczema.

Proprietary Preparations

Collone HV (*ABM Chemicals, UK*). An emulsifying wax consisting of a fatty alcohol with added saponifiable fats. Collone SE. An emulsifying wax similar to emulsifying wax *B.P.* Collone SEC. A brand of emulsifying wax *B.P.*

Crodex A (*Croda, UK*). A brand of emulsifying wax.

Cyclochem (*Witco, UK*). A range of anionic self-emulsifying waxes.

Cyclonette Wax (*Witco, UK*). A brand of emulsifying wax.

Empiwax SK (*Albright & Wilson, Marchon Division, UK*). A brand of emulsifying wax. Empiwax SK/BP. A brand of emulsifying wax *B.P.*

HEB Simplex (formerly known as Halden's Emulsifying Base) (*Waterhouse, UK*). Contains 3 parts of liquid paraffin, 2 parts of white soft paraffin, and 2 parts of a mixture of higher fatty alcohols (hexadecyl and octadecyl alcohols) containing 10% of their acid esters (phosphates). HEB Lac is a stabilised emulsion of HEB Simplex in water.

A cream containing 5% of HEB Simplex in water had an average oil-globule size of 5 μm when homogenised, compared with 50 μm when prepared by agitation and cooling. The addition of 1% of cetostearyl alcohol or cetomacrogol might facilitate the production of a fine-texture cream.— *Chemist Druggist*, 1968, *190*, 238.

Lanette Wax SX (*Ronsheim & Moore, UK*). An anionic self-emulsifying wax consisting of a mixture of sodium alkyl sulphate and cetyl and stearyl alcohols, giving more viscous emulsions than those produced by emulsifying wax. Lanette Wax SX B.P. A brand of emulsifying wax.

Silcock's Base (*Bonfield, Eire*). Emulsifying wax 15%, white soft paraffin 20%, methyl hydroxybenzoate 0.25%, propyl hydroxybenzoate 0.25%, and water to 100%.

6022-f

Magnesium Stearate (*B.P., Eur. P., U.S.N.F.*). Mag. Stear.; Magnesii Stearas; Estearato de Magnésio.

CAS — 557-04-0 (stearate); 2601-98-1 (palmitate).

Pharmacopoeias. In *Arg., Aust., Br., Braz., Chin., Cz., Eur., Fr., Ger., Hung., It., Jap., Jug., Neth., Nord., Pol., Port., Roum.*, and *Swiss.* Also in *U.S.N.F.*

The magnesium salt of a commercial stearic acid. It consists chiefly of a mixture of magnesium stearate and magnesium palmitate and contains 3.8 to 5% of Mg. *U.S.N.F.* describes a compound of magnesium with a mixture of solid organic acids obtained from fats consisting chiefly of magnesium stearate and magnesium palmitate, containing the equivalent of 6.8 to 8% of MgO, and losing not more than 4% of its weight when dried.

It is a fine, white, bulky, impalpable, unctuous powder, tasteless and odourless or with a faint odour of stearic acid. It adheres readily to the skin. It loses not more than 6% of its weight when dried. It is available in grades with different apparent volumes. Practically insoluble in water, alcohol, acetone, and ether. The filtrate from 1 g boiled for 1 minute with 20 ml of water has a pH of 6.2 to 7.4. Incompatible with acids and iron salts. Store in airtight containers.

Adverse Effects. Deaths have occurred from accidental inhalation of baby dusting powders containing magnesium stearate.

Uses. Magnesium stearate is used as a dusting-powder in skin diseases, and in cosmetics. In barrier creams the powder gives body to the cream and acts as a mechanical barrier to chemical irritants. It is dusted around fistulas to prevent excoriation. It is also added as a lubricant to the granules in tablet-making.

6023-d

Sodium Cetostearyl Sulphate. Natrium Cetylosulphuricum; Natrium Cetylstearylosulphuricum; Cetylstearylschwefelsaures Natrium.

CAS — 1120-01-0 (sodium cetyl sulphate); 1120-04-3 (sodium stearyl sulphate).

Pharmacopoeias. In *Aust., Belg., Cz., Ger.*, and *Roum.*

A mixture of approximately equal parts of sodium cetyl sulphate, $C_{16}H_{33}NaO_4S$, and sodium stearyl sulphate, $C_{18}H_{37}NaO_4S$.

It is a white or pale yellow amorphous or crystalline powder with a slight odour and a characteristic taste. Soluble in water, forming a foaming turbid solution; partly soluble in alcohol. Protect from light.

Sodium cetostearyl sulphate is used for the same purposes as sodium lauryl sulphate, see below.

Proprietary Names
Lanette E (*Deutsche Hydrierwerke, Ger.*).

6024-n

Sodium Lauryl Sulphate (*B.P.*). Sodium Lauryl Sulfate (*U.S.N.F.*); Sod. Lauryl Sulph.; Natrium Laurylsulphuricum; Sodium Laurilsulfate.

CAS — 151-21-3.

Pharmacopoeias. In *Aust., Br., Braz., Cz., Hung., Ind., It., Jap., Jug., Pol., Roum.*, and *Swiss.* Also in *U.S.N.F.*

A mixture of sodium normal primary alkyl sulphates, consisting mainly of sodium dodecyl sulphate, $C_{12}H_{25}O.SO_2.ONa$. *B.P.* specifies that the mixture contains not less than 85% of sodium alkyl sulphates and both *B.P.* and *U.S.N.F.* specify not more than a total of 8% of sodium chloride and sodium sulphate.

It is a white or pale yellow sternutatory powder or crystals with a slight characteristic odour. Soluble 1 in 10 of water giving a turbid solution; partly soluble in alcohol; practically insoluble in chloroform, ether, and light petroleum. Incompatible with cationic materials and with acids below pH 2.5.

Hydrolysis. Practically no hydrolysis occurred in solutions of sodium lauryl sulphate at pH 4 and above. Below pH 2.5, hydrolysis to lauryl alcohol and sodium acid sulphate was accelerated; the rate of hydrolysis also varied with the temperature and the concentration.— R. R. Read and W. G. Fredell, *Drug Cosmet. Ind.*, 1959, *84*, 178.

Adverse Effects. Sodium lauryl sulphate may be irritant to the skin.

Hydrophilic ointment and sodium lauryl sulphate 1% in a similar basis produced contact irritant dermatitis when applied topically under occlusive dressings for 16 hours a day for more than 3 days.— P. R. Bergstresser and W. H. Eaglestein, *Archs Derm.*, 1973, *108*, 218, per *J. Am. med. Ass.*, 1973, *225*, 1140.

Intravenous toxicity. As a result of experiments on *animals*, it was concluded that sodium lauryl sulphate, whose adverse effects included marked toxic action on lungs, kidneys, and liver, should not be used intravenously in man.— H. F. Cascorbi *et al.*, *J. pharm. Sci.*, 1963, *52*, 803.

Uses. Sodium lauryl sulphate is an anionic emulsifying agent. It reduces surface tension and is a detergent and wetting agent, effective in both acid and alkaline solution and in hard water. It is used in medicated shampoos and as a skin cleanser. It is used in the preparation of Emulsifying Wax (see p.1441).

Magnesium lauryl sulphate is used as a [illegible] in tablets.

The use of a detergent alkaline douche [illegible] sodium lauryl sulphate, sodium perborate, and borate (pH 9.3) was of benefit in patients [illegible] tious vaginitis by relieving pruritus.— R. S. [illegible] *al., Curr. ther. Res.*, 1973, *15*, 839.

Magnesium lauryl sulphate. Magnesium lauryl [illegible] was equivalent to magnesium stearate as a [illegible] Tablet and capsule disintegration was faster [illegible] nesium lauryl sulphate than with the stearate. Caldwell and W. J. Westlake, *Can. J. pharm. Sci.*, 1973, *8*, 50.

Further references: A. M. Salpekar and L. [illegible] burger, *J. pharm. Sci.*, 1974, *63*, 289.

Proprietary Preparations of Alkyl Sulphates
Some Other Anionic Surfactants

Cycloryl 580 and 585N (*Witco, UK*). Brands of lauryl sulphate.

Empicol (*Albright & Wilson, Marchon Div.*). A range of alkyl and alkyl ether sulphates. Empicol AL30 (ammonium lauryl sulphate), Empicol DLS (diethanolamine lauryl sulphate), Empicol series of sodium lauryl ether sulphates), Empicol series of monoethanolamine lauryl sulphates, LM, LX, LZ (series of sodium lauryl sulphates), Empicol ML26 (magnesium lauryl sulphate), and TL40 (triethanolamine lauryl sulphate).

Neopon (*Witco, UK*). A range of alkyl sulphates, alkyl ether sulphates.

Pentrones (*ABM Chemicals, UK*). A range of surfactants including Pentrone A (a series of [illegible] salts of alkyl aryl sulphonic acids), and Pentrone [illegible] series of sodium salts of sulphosuccinate derivatives.

Rewopols (*Rewo, UK*). A range of anionic and [illegible] surfactants. The anionic surfactants include [illegible] based on alkyl sulphates, alkyl and alkylphenol sulphates, derivatives of sulphosuccinates, and [illegible] namates, and alkyl aryl sulphonates.

Solumins (*ABM Chemicals, UK*). A range of [illegible] surfactants including Solumins FPnS and FNaS [illegible] of the sodium salts of sulphated alkyl [illegible] polyethoxyethanols), Solumins TnS (a series of [illegible] salts of sulphated ethoxylated fatty alcohols which are used as detergents in surgical [illegible] Solumins PFN (a series of phosphate esters of [illegible] lated alkyl phenols).

Sulphonated Lorol Powder DC (*Ronsheim & [illegible] UK*). A brand of sodium lauryl sulphate, available [illegible] spray-dried powder containing 90% of sodium [illegible] phates. Sulphonated Lorol Liquid TA. Contains [illegible] triethanolamine lauryl sulphate 40% in aqueous [illegible] Sulphonated Lorol Paste. Contains technical [illegible] lauryl sulphate 40 to 45% and water about 50%.

Teepol (*Shell Chemicals*). A range of aqueous [illegible] solutions based on sodium alkyl benzene [illegible] alcohol ether sulphate, and alcohol ethoxylate.

NOTE. A grade of Teepol was described in the *B.P. 1949* under the name Sulphestol Solution.

Antimist solutions for spectacles. (1) Sodium [illegible] 1 g, glycerol 10 ml, Teepol 5 ml, water to 100 [illegible] Teepol 25 ml, industrial methylated spirit 10 ml, to 100 ml. A few drops of the solution were applied the glass which was then rubbed bright; the [illegible] lasted several hours.— *Br. med. J.*, 1961, *2*, 841.

Other Proprietary Names of Sodium Lauryl Sulphate
Anticerumen (*Spain*).

Sodium lauryl sulphate was also formerly marketed in Great Britain under the proprietary name Manoxol Powder LK (*Onyx Chemical Co., USA*). A preparation containing triethanolamine ammonium lauryl sulphate was formerly marketed under the proprietary name ProDermide (*Kerfoot*).

6025-h

Sodium Oleate.
$C_{18}H_{33}NaO_2 = 304.4$.

CAS — 143-19-1.

A yellowish-white fatty solid with a faint odour of acid. Soluble 1 in 10 of water and 1 in 20 of alcohol.

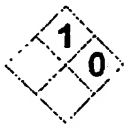
Sodium oleate has been used as an ingredient in preparations for the symptomatic relief of haemorrhoids and pruritus ani. It was also formerly used as a [illegible] ogue.

Oct-22-98

SPECTRUM®

ISO 9002 CERTIFIED Gardena, CA

Material Safety Data Sheet

NFPA	HMIS	Personal Protective Equipment
	Health Hazard 1 Fire Hazard 1 Reactivity 0	 See Section 15.

Section 1. Chemical Product and Company Identification

Common Name/ Trade Name	Magnesium stearate	Code	M3190
		CAS#	557-04-0
Manufacturer	SPECTRUM QUALITY PRODUCTS 14422 SOUTH SAN PEDRO STREET GARDENA, CALIFORNIA 90248-9985	RTECS	WI4390000
		TSCA	On the TSCA list.
Commercial Name(s)	Not available	CI#	Not available.
Synonym	Octadecanoic acid, magnesium salt	In case of emergency	
Chemical Name		CHEMTREC (24hr) 800-424-9300	
Chemical Family	Not available.	Emergency phone: (310) 516-8000	
Chemical Formula	(C17H35COO)2Mg		
Supplier	SPECTRUM QUALITY PRODUCTS 14422 S. SAN PEDRO STREET GARDENA, CA 90248-9985		

Section 2. Composition and Information on Ingredients

		Exposure Limits			
Name	CAS#	TWA (mg/m3)	STEL (mg/m3)	CEIL (mg/m3)	% by Weigh
Magnesium stearate	557-04-0				100

Toxicological Data on Ingredients: Magnesium stearate:

Section 3. Hazards Identification

Potential Acute Health Effects: Slightly dangerous to dangerous in case of ingestion. Very slightly to slightly dangerous in case of skin contact (irritant), of eye contact (irritant), of inhalation.

Potential Chronic: CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. Toxicity of the product to the reproductive system: Not available. There

Health Effects	known to aggravate medical condition.

Federal and State Regulations	WARNING: This product contains a chemical known to the State of California to cause cancer. Chemical ingredient(s) requiring this warning: NONE WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm. Chemical ingredient(s) requiring this warning: NONE

Section 4. First Aid Measures

Eye Contact	IMMEDIATELY flush eyes with running water for at least 15 minutes, keeping eyelids open. COLD water may be used.
Skin Contact	If the chemical got onto the clothed portion of the body, remove the contaminated clothes as quickly as possible, protecting your own hands and body. Place the victim under a deluge shower. If the chemical touches the victim's exposed skin, such as the hands: Gently and thoroughly wash the contaminated skin with running water and non-abrasive soap. Be particularly careful to clean folds, crevices, creases and groin. Cover the irritated skin with an emollient. If irritation persists, seek medical attention. Wash contaminated clothing before reusing.
Hazardous Skin Contact	No additional information.
Inhalation	Allow the victim to rest in a well ventilated area. Seek immediate medical attention.
Hazardous Inhalation	No additional information.
Ingestion	Remove dentures if any. Have conscious person drink several glasses of water or milk. INDUCE VOMITING by sticking finger in throat. Lower the head so that the vomit will not reenter the mouth and throat. NEVER give an unconscious person anything to ingest. Seek medical attention.
Hazardous Ingestion	No additional information.

Magnesium Stearate

1. Nonproprietary Names

BP: Magnesium stearate
PhEur: Magnesii stearas
USPNF: Magnesium stearate

2. Synonyms

E572; *HyQual*; magnesium octadecanoate; stearic acid magnesium salt.

3. Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

4. Empirical Formula Molecular Weight

$C_{36}H_{70}MgO_4$ 591.27
(for pure material)

The USPNF XVII describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids obtained from fats and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The BP 1993 and PhEur 1983 describe magnesium stearate as consisting mainly of magnesium stearate with variable proportions of magnesium palmitate and magnesium oleate ($C_{36}H_{66}MgO_4$).

5. Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

6. Functional Category

Tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0%.

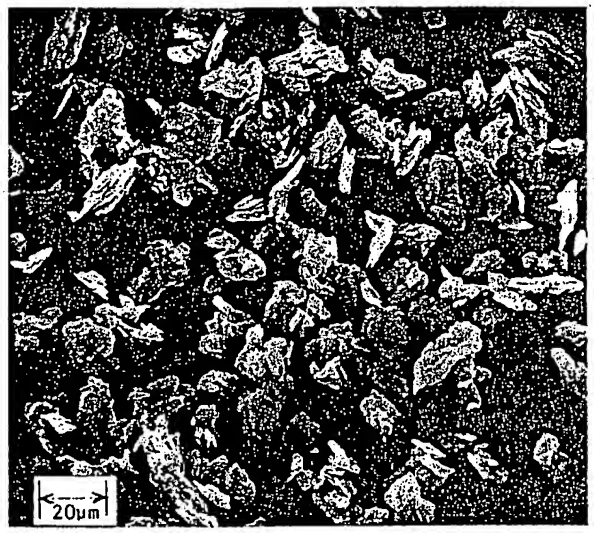
8. Description

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint, characteristic odor and taste. The powder is greasy to the touch and readily adheres to the skin.

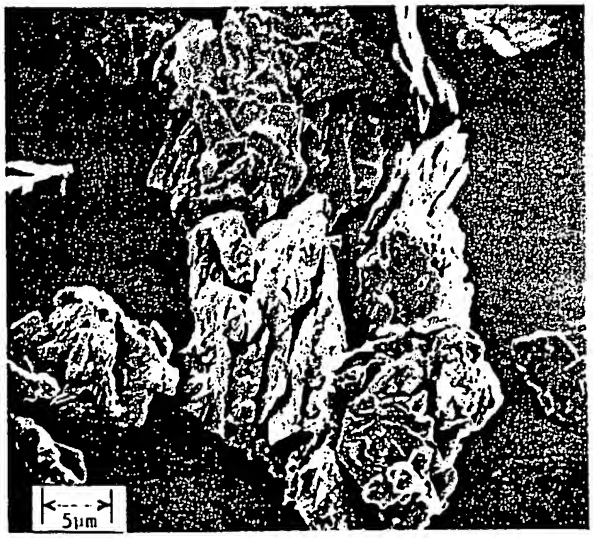
9. Pharmacopeial Specifications

Test	PhEur 1983	USPNF XVII (Suppl 9)
Identification	+	+
Microbial limits	—	+
Acidity or alkalinity	+	—
Color of solution	+	—
Acid value of the fatty acids	195-210	—
Clarity and color of solution of the fatty acids	+	—
Loss on drying	⩽ 6.0%	⩽ 4.0%
Heavy metals	⩽ 20 ppm	—
Lead	—	⩽ 0.001%
Organic volatile impurities	—	+
Chloride	⩽ 250 ppm	—
Sulfate	⩽ 0.5%	—
Assay (dried basis, as Mg)	3.8-5.0%	—
Assay (as MgO)	—	6.8-8.3%

SEM: 1
Excipient: Magnesium stearate
Magnification: 600x



SEM: 2
Excipient: Magnesium stearate
Magnification: 2400x



10. Typical Properties

Compressibility: *see* HPE Data.
Density: 1.03-1.08 g/cm^3, *see also* HPE Data.
Density (tapped): 0.30 g/cm^3, *see also* HPE Data.
Flash point: 250°C
Flowability: poorly flowing, cohesive powder.
Melting point: 88.5°C
Moisture content: *see* HPE Data.
Polymorphism: a trihydrate, acicular form and a dihydrate, lamellar form have been isolated, with the latter possessing the better lubricating properties.
Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%). *See also* HPE Data.
Specific surface area: 2.45-16.0 m^2/g.

HPE Laboratory Data

	Method	Lab #	Results
Compressibility			
at 63.5-235 MPa	COM-1	21	No compacts [a]
at 500 MPa	COM-7	12	Lamination [b]
Density	DE-1	7	1.06-1.1 g/cm^3 [b]
Density (bulk & tapped)	BTD-2	1	B: 0.143 g/cm^3 [b]
			T: 0.224 g/cm^3 [b]
Density (bulk & tapped)	BTD-7	14	B: 0.160 g/cm^3 [b]
			T: 0.180 g/cm^3 [b]
Moisture content	EMC-1	5	*See* Fig. 1. [c]
Moisture content	MC-12	1	3.85% [b]
Moisture content	MC-12	5	3.00% [c]
Solubility			
Ethanol (95%) at 25°C	SOL-1	1	0.160 mg/mL [b]
n-Hexane at 25°C	SOL-1	1	0.018 mg/mL [b]
Water at 25°C	SOL-1	1	0.040 mg/mL [b]

Supplier:
a. Witco Corporation;
b. Mallinckrodt Speciality Chemicals Co;
c. Penick (Lot No.: 338-NB5-003).

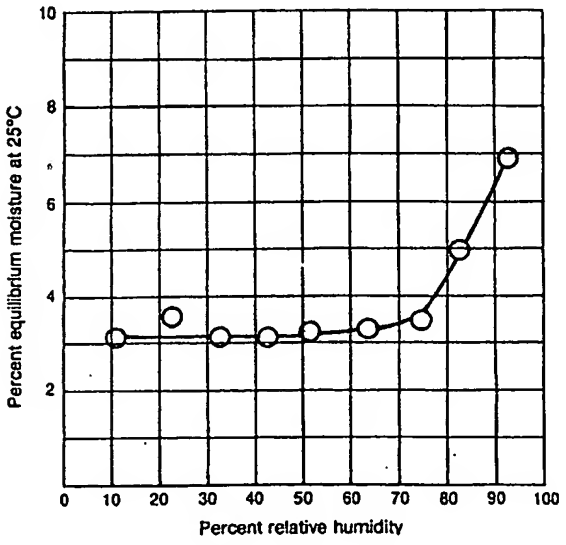


Fig. 1: Equilibrium moisture content of magnesium stearate.

11. Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials.

13. Method of Manufacture

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate, or by the interaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures.

14. Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation. Inhalation of magnesium stearate powder is harmful and has resulted in fatalities, *see also* Section 15.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Belg, Br, Braz, Chin, Cz, Eur, Fr, Ger, Hung, Ind, It, Jpn, Mex, Neth, Nord, Port, Rom, Swiss, Yug and USPNF.

18. Related Substances

Calcium Stearate; Stearic Acid; Zinc Stearate.

19. Comments

Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations.[1-6] Since there may be variation between batches of magnesium stearate, it has not been possible to conclusively correlate the dissolution rate retardation with the observed lubricity.[7] The physical properties of different batches of magnesium stearate, such as specific surface area, have however been correlated with lubricant efficacy.[8-11]
There is evidence to suggest that the hydrophobic nature of magnesium stearate can vary from batch to batch due to the presence of water-soluble, surface-active impurities such as sodium stearate. Batches containing very low concentrations of these impurities have been shown to retard the dissolution of a drug to a greater extent than when using batches which contain higher levels of impurities.
An increase in the coefficient of variation of mixing and a decrease in the dissolution rate has been observed following blending of magnesium stearate with a tablet granulation. Tablet dissolution rate and crushing strength decreased as the time of blending increased; magnesium stearate may also

increase tablet friability. Blending times with magnesium stearate should thus be carefully controlled.[12-26]

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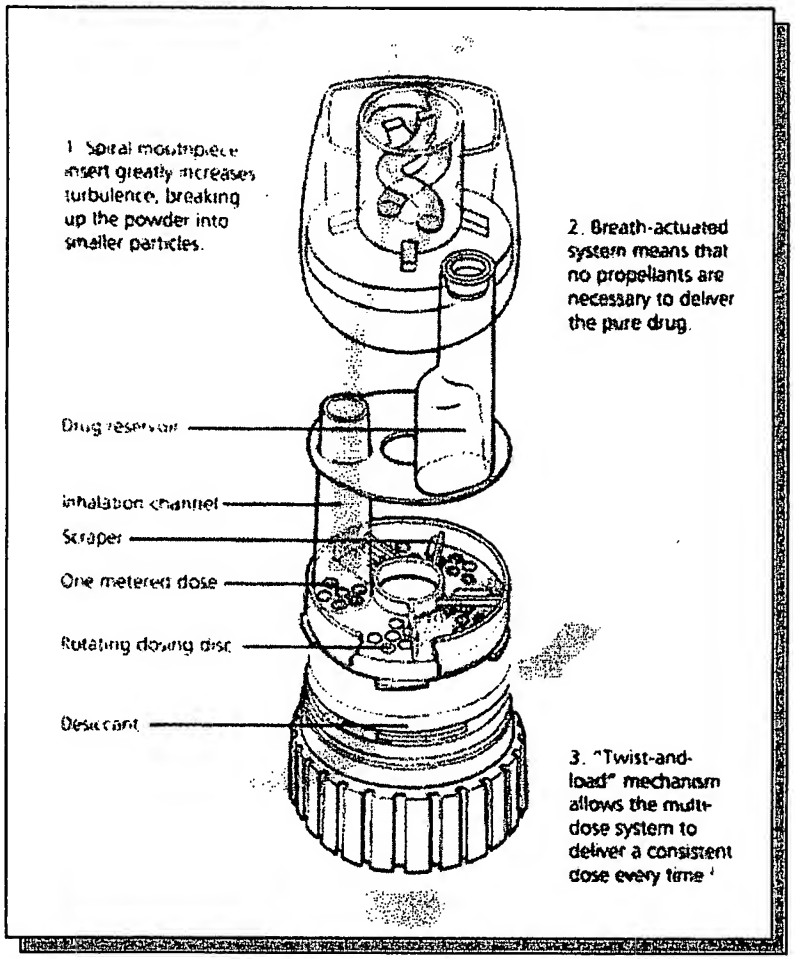
22. Authors

USA: LV Allen, PE Luner.

The Turbuhaler (Astra)



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